SCIENTIFIC ABSTRACT

This is a phase I pilot study to determine the safety and feasibility of gene transfer of RNA-based anti-HIV therapy expressed in lentivirus-transduced hematopoietic progenitor cells (HPC) in patients undergoing autologous stem cell transplantation (HCT) for poor-prognosis AIDS lymphoma (ARL). The lentivirus vector encodes 3 forms of anti-HIV RNA: RNAi in the form of a short hairpin RNA (shRNA) targeted to an overlapping exon in HIV-1 *tat* and *rev* (shI), an RNA decoy for the HIV TAT-reactive element (TAR), and a ribozyme that targets the host cell CCR5 cytokine receptor (CCR5RZ). The vector, to be used to transduce autologous CD34-selected HPC, is called rHIV7-shI-TAR-CCR5RZ, has a self-inactivating vector design, and will be produced at the Beckman Research Institute at City of Hope. The rHIV7-shI-TAR-CCR5RZ-transduced CD34+ HPC is the research agent. The primary aims of the study are safety and feasibility, and the secondary aims are the assessments of the duration of detectible transduced cells in blood and marrow and of any effect on HIV-1 infection.

Patients with ARL, who agree to participate, will have peripheral HPC mobilized and collected by apheresis (HPC-A), apportioned into a routine "unmanipulated" pool of HPC-A cells and a research pool of HPC-A cells for genetic transduction. The unmanipulated cells will be cryopreserved until the time of HCT. From the research pool, CD34+ cells will be selected using a Miltenyi CliniMax™ system, and then cryopreserved until the time of transduction just prior to HCT. Near the end of the final dose-intense lymphoma chemotherapy (carmustine, etoposide, and cyclophosphamide), the research pool will be thawed and transduced with rHIV7-shI-TAR-CCR5RZ, and infused. The unmanipulated autologous HPC-A cells will be infused on the next day as standard-of-care HCT. The research participants will be then be followed for engraftment of the transplanted cells, for adverse events, for evidence of RNA expression and DNA marking by the transgene in the peripheral blood cells over time, and for transgene integration site analyses in the peripheral blood cells. The HIV-1 infection status will be monitored with routine tests of HIV-1 plasma RNA and CD4 counts, and detectible endogenous HIV-1 RNA will be evaluated for evidence of recombination events with the transgene sequences. The results of this study will help to answer the question of whether this new lentivirus-based strategy of gene transfer deserves further evaluation as an eventual method for control of HIV/AIDS.